REMARKS

Claims 1-9, 11-19 and 24 are currently pending. Applicants have cancelled claims 2-9 and 13 without prejudice or disclaimer of any of the subject matter contained therein. Accordingly, claims 1, 11-12, 14-19 and 24 remain in the application.

To further prosecution, Applicants have amended Claims 1 and 11 to include a pharmaceutical composition comprising activated protein C, a diluent and a chelating agent, wherein the composition is in a vial or I.V. bag, is suitable for direct administration to a patient, and has reduced or eliminated any increase in 1-149 aPC light chain variant 24 hours after preparation of the composition (Claim 11 to where the light chain variant does not increase by more than 2%). Support for the amendments is found throughout the specification, specifically at page 2 lines 25-29, page 6 lines 6-8, Table 1A page 14, Table 1B page 15 and Table 2B page 18. Applicants have also amended the dependency of the previously presented claims 11-12, 14 and 24. Support for the amendments is found throughout the specification, specifically at page 2 lines 26-27 for claims 11-12, page 5 lines 16-25 for claim 14 and page 3 lines 10-11 for claim 24. Applicants respectfully request entry of the amendments and submit that no new matter is added.

REJECTION OF CLAIMS 1, 11-12, 14-19 UNDER 35 U.S.C. § 102 (b) IN VIEW OF CARLSON ET AL. (CARLSON)

Claims 1, 11-12, 14-19 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Carlson et al., U.S. Patent No. 6,159,468 (Carlson). The Examiner states that Carlson teaches a composition comprising human protein C, 0.4M sodium chloride, and 20mM Tris-acetate, pH 6.5 (Preparation 1); Preparation 1 is made 5mM in EDTA and passed over a thrombin column, thus activating protein C, and eluted with Tris buffer and lyophilized (Preparation 2). Preparation 2 therefore comprises activated protein C, EDTA (a chelator; see column 7, lines 1-2), Tris-acetate, and sodium chloride at pH 6.5 (column 7, lines 26-27; Example 1).

Applicants have amended Claim 1 to include a pharmaceutical composition comprising activated protein C, a diluent and a chelating agent, wherein the composition is in a vial or I.V. bag, is suitable for direct administration to a patient, and has reduced or eliminated any increase in 1-149 aPC light chain variant 24 hours after preparation of the composition. Carlson does not teach all the limitations of the claim as amended. For

example, Carlson does not teach a composition that has reduced or eliminated any increase in 1-149 aPC light chain variant 24 hours after preparation of the composition.

Applicants draw Examiners attention to Table 1a and Table 1b of Example 1 (page(s) 14 and 15, respectively) and Table 2b of Example 2 (page 18). The tables clearly demonstrate that addition of a diluent, without any EDTA to an aPC formulation (which as the Examiner states contains some EDTA from the purification steps of preparation 2 of this application, which is similar to the preparation 2 in Carlson) causes aPC degradation and forms the less active 1-149 light chain variants ranging from 19% to 79% after 24 hours. These variants are however not detectable after the addition of various amounts of EDTA to the aPC composition as claimed by the Applicant. Therefore, Carlson does not teach the claimed invention and withdrawal of this rejection is requested.

REJECTION OF CLAIMS 1 11 and 12 UNDER 35 U.S.C. § 102(b) IN VIEW OF FOSTER ET AL. (FOSTER)

Claims 1, 11 and 12 are rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Foster et al., U.S. Patent No. 5,516,650 (Foster) taken in light of Carlson et al. The Examiner states that Foster teaches a solution comprising activated protein C, EDTA (a chelating agent), and TBS (Tris-buffered saline) in water (column 21, lines 20-24). Carlson is cited as evidence that Tris is a pharmaceutically acceptable buffer (column 3, lines 9-12).

Applicants point out that in light of the amendments, Foster does not teach all the limitations of the claimed invention. Foster teaches a method of purifying a ***variant form of activated protein C*** that encodes a cleavage site sequence constructed by mutagenesis (column 19 lines 55-61) from media using a monoclonal antibody column specific for calcium-induced conformation of protein C, and an elution buffer of TBS containing EDTA. Even if a person skilled in the art would consider Foster relevant to Applicants invention, Carlson does not anticipate a pharmaceutical composition comprising activated protein C, a diluent and a chelating agent, wherein the composition is in a vial or I.V. bag, is suitable for direct administration to a patient, and has reduced or eliminated any increase in 1-149 aPC light chain variant 24 hours after preparation of the composition. Withdrawal of this rejection is requested

REJECTION OF CLAIMS 1, 11-12, 14-19 and 24 UNDER 35 U.S.C. § 103(a) IN VIEW OF CARLSON

Claims 1, 11-12, 14-19 and 24 are also rejected under 35 U.S.C § 103(a) as being allegedly unpatentable over Carlson. The rejection alleges that while the composition of Carlson comprises some EDTA from the activation step (column 7, lines 1-3), a person of ordinary skill in the art would have had a reasonable expectation of success in *including additional EDTA in the composition of Carlson because EDTA is taught by Carlson not to affect the composition's essential properties. The skilled artisan would have been motivated to include additional EDTA for the expected benefit that activated protein C would be protected from calcium and other divalent ions (page 9).* It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was made to include additional EDTA in the composition of Carlson because Carlson suggest its inclusion to chelate metal ions.

Applicants respectfully traverse this rejection. Applicants reiterate that the EDTA in Carlson was added prior to the lyophilization of aPC during the purification process to prevent premature thrombin formation and cleavage of Protein C Zymogen by thrombin. After the Protein C Zymogen is converted to aPC by passing it over a bovine thrombin column, and any leached thrombin is subsequently removed by an anion exchange resin (page 12, line 15-17) a person of ordinary skill in the art would not have any reason to add additional EDTA to lyophilized aPC, *even if EDTA does not affect the compositions essential properties.* Nowhere does Carlson teach or suggest a need for or advantage from additional EDTA in the composition after the purification process and lyophilization. Moreover, Carlson does not teach the existence of light chain degradation aPC variants or the propensity of lyophilized activated protein C to form these light chain truncated variants after the addition of a diluent. Carlson is silent on the effects the metal ions or chelating agents may have on the propensity of activated protein C to form such truncated variants. The rejection fails to articulate the basis on which one skilled in the art would have been motivated to add a chelating agent to be used with aPC to reduce its propensity to degrade. There must be some articulated reasoning with some underpinning to support the legal conclusion of obviousness.

Applicants point out that they discovered the 1-149 light chain aPC degradation variant was less active than other previously identified aPC variants and was primarily responsible for the decreased potency of aPC in-use solutions. Applicants further discovered

that the addition of a chelating agent to the aPC composition provide a means for sequestering metals that would otherwise promote aPC degradation to these less active 1-149 light chain variants. The rejection fails to identify any suggestion or incentive in Carlson to add a chelating agent with the diluent to improve the solution stability of aPC. In contrast, Tables 1A (page 14), 1B (page 15) and 2B (page 18) in the Examples of the application clearly demonstrate that addition of a diluent without any EDTA to an aPC formulation (which the examiner claims contains some EDTA from the purification steps of preparation 2) causes aPC degradation and forms the less active 1-149 light chain variants ranging from 19% to 79% after 24 hours. These variants are however not detectable after the addition of various amounts of additional EDTA to the aPC formulation as claimed by the Applicant. Therefore the addition of a chelating agent to the in-use aPC formulation clearly results in a patentable difference in the composition to that of Carlson by providing increased stability to the aPC in-use solutions.

For the reasons stated above, Applicants submit that the Examiner has failed to set forth a prima facie case and withdrawal of this rejection is respectfully requested.

CONCLUSION

Having addressed all outstanding issues, Applicants respectfully request entry and consideration of the foregoing amendments that place the application in condition for allowance. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is invited to telephone the undersigned at the number below.

Respectfully submitted,

/Brian P. Barrett/

Brian P. Barrett
Registration No. 39,597
Phone: 317-276-7243

Eli Lilly and Company
Patent Division
P.O. Box 6288
Indianapolis, Indiana 46206-6288

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